UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,440	02/05/2004	Michal Daniely	26003	3178

7590 12/27/2006

Martin D. Moynihan
PRTSI, Inc.
P. O. Box 16446
Arlington, VA 22215

EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,440	DANIELY ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *1-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The election filed October 19, 2006, is acknowledged and has been entered.

Applicant has elected the invention of Group XIX, namely Claims 38-41, 42, 46, 48, 54, 56-58, 59, 63, 65 and 71, drawn to a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample comprising staining cells with at least two stains, wherein one stain is a morphological stain and one stain is an in situ hybridization stain and imaging the cells.

2. Claims 1-71 are pending in the application. Claims 1-36 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Due to the rejoinder of Groups XVI-XXX detailed below, claims 37-71 are under examination.

Election/Restrictions

4. Upon further consideration of the restriction and election requirement set forth in the Office action mailed August 22, 2006, claims drawn to the inventions of Groups XVI-XXX have been rejoined with claims drawn to the elected invention. The restriction and election requirement separating these inventions has been withdrawn.

Priority

5. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of the U.S. Provisional Application No. 60/459,992, filed April 4, 2003, is acknowledged.

However, claims 37-71 do not properly benefit from the earlier filing because, for example, the instant claims recite the limitation "at least two stains", which is interpreted

as two or more stains and support for using more than two stains was not found in U.S. Provisional Application No. 60/459,992.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely February 5, 2004.

Declaration

6. The oath or declaration is defective because: It does not correctly identify the city of residence and the city of the post office address of each inventor. In this case, the city of residence and the city of the post office address for inventor Eran Kaplan are incomplete as several letters in the city name appear to be missing. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

Specification

7. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because of the following typographical error that occurs on page 9, line 27, "abovementioned".

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 37-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 37-71 are indefinite because claims 37 and 55 recite the limitation "sequentially and/or simultaneously". Since this is read to encompass "sequentially and simultaneously" exposing said stained nucleated cells to a least two imaging modes, it is unclear how the cells can be exposed to the imaging modes both one after the other and at the same time.

It is suggested this issue be remedied by amending claim 37, for example, to recite, "sequentially or simultaneously", if such subject matter is regarded as the invention and the suggested claim language finds written support in the specification, as filed.

(b) Claims 41-47 and 58-64 are indefinite because claims 41 and 58 recite that the two stains are selected "independently" from the group consisting of a morphological stain, an immunological stain, an activity stain, a cytogenetical stain, an in situ hybridization stain and a DNA stain. On what basis are the two stains selected from the group? Does one randomly choose two of the stains, or is some other basis used? Furthermore, if a one type of stain is selected for the first stain, is that same type of stain a possible choice for the second stain? It thus submitted that the metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained, as it cannot be determined how the recitation is intended to further limit the subject matter of the preceding claims. As such, the claims fail to delineate the subject matter that is the invention with the requisite degree of clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claims 48-53 and 65-70 recites the limitation "a first stain" and "a second stain". However, claims 37 and 55 from which these claims depend do not recite any order of stains and it is unclear whether more than one "first stain" or more that one "second stain" is being contemplated. Therefore, there is insufficient antecedent basis

for this limitation in the claim. Amending the claims to recite "one stain" and "another stain" would obviate this rejection.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 37-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the

applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

Claims 37-71 are directed to methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer using at least two members of a genus of "stains". Some of the claims are further directed to stains, which are "morphological stains", "immunological stains", "cytogenetical stains", "*in situ* hybridization stains" or "DNA stains". According to the disclosure and/or claims, the morphological stains include a May-Grunwald-Giemsa stain, a Giemsa stain, a Papanicolau stain, a Hematoxylin-Eosin

stain, and a DAPI stain. The immunological stains include fluorescently labeled immunohistochemistry stains, radiolabeled immunohistochemistry stains, and immunocytochemistry stains. The activity stains include cytochemical stains, and substrate binding assay stains. The cytogenetical stains include G-banding stains, R-banding stains, Q-banding stains, and C-banding stains. The *in situ* hybridization stains inlcude fluorescent *in situ* hybridization stains, radiolabeled *in situ* hybridization stains, digoxigenin labeled *in situ* hybridization stains, and biotinylated *in situ* hybridization stains. The DNA stains include DNA-binding fluorescent dyes.

The specification teaches that stains suitable for identifying transitional cell carcinoma or diagnosing bladder cancer are morphological stains, immunological stains, activity stains, cytogenetical stains, *in situ* hybridization stains or DNA stains. The specification further teaches examples of morphological, immunological, activity, cytogenetical, *in situ* hybridization and DNA stains, such as May-Grunwald-Giemsa stain, Giemsa stain, Papanicolau stain, Hematoxylin-Eosin stain, DAPI stain, fluorescently labeled immunohistochemistry stains, radiolabeled immunohistochemistry stains, immunocytochemistry stains, cytochemical stains, substrate binding assay stains, G-banding stains, R-banding stains, Q-banding stains, C-banding stains, fluorescent *in situ* hybridization stains, radiolabeled *in situ* hybridization stains, Digoxigenin labeled *in situ* hybridization stains, biotinylated *in situ* hybridization stains, propidium iodide stain and ethidium bromide stain (see page 11, line 22 to page 14, line 29).

The specification, however, does not describe the structure of a sufficient number of species of the genus of "stains", or a sufficient number of species of any of the subgenera of morphological stains, immunological stains, activity stains, cytogenetical stains, in situ hybridization stains or DNA stains to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Conn's Biological Stains, 10th Edition (edited by Horobin et al, May 2002) teaches common aromatic ring systems that are found in stains, but which are not described in the specification (see page 2, Figure 1.1). Furthermore, Conn's Biological Stains

teaches that the structure of a stain and its function are not necessarily related. For example, Conn's Biological Stains teaches Alizain red S, Nuclear fast red, and carminic acid share a common core structure as anionic anthraquinone dyes, yet are functionally distinct, and thus have different uses. In particular, Alizarin red S is used to "stain" or detect calcium ions, whereas nuclear fast red is used to stain nuclei, and carminic acid is used to stain glycogen (see pages 370-374).

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). In this instance, while the specification describes the structure of some stains that may be considered morphological stains, immunological stains, activity stains, cytogenetical stains, in situ hybridization stains or DNA stains, these stains do not share a common structure and as evidenced by Conn's Biological Stains (supra), one cannot predict the structure of a stain from a given function and vice versa.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). Here, there is no language that adequately describes the genus of stains to which the claims are directed, or the subgenera of morphological stains, immunological stains, activity stains, cytogenetical stains, in situ hybridization stains or DNA stains.

Again, the genus of stains and the subgenera of morphological stains, immunological stains, activity stains, cytogenetical stains, in situ hybridization stains and DNA stains all do not share common structural features that relate to their stated functions.

What structural and/or functional features define members of the genus of "morphological stains"? How are such stains structurally and/or functionally distinct from, for example, members of the genus of "activity stains"? How does one "stain" an activity? How are "cytogenetical stains" different from "DNA stains"?

Given the lack of particularity with which the "stains" to which the claims are directed are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of "stains" or the subgenera of "morphological stains", "immunological stains", "activity stains", "cytogenetical stains", "in situ hybridization stains" and "DNA stains" to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 37-48, 51-65 and 68-71 are rejected under 35 U.S.C. 102(a) as being anticipated by Daniely et al (Annales de Genetique, 46:153, September 2003) as evidenced by Shimoni et al (Leukemia, 16:1413-1418, August 2002), Skacel et al (Anal Quant Cytol Histol, 23(6): 381-387, December 2001).

The claims are drawn to a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of a urine sample with at least two stains and sequentially or simultaneously exposing said stained cells to at least two imaging modes to identify transitional cell carcinoma cells or diagnose bladder cancer. The claims are further drawn to the each of the stains being either a morphological stain, an immunological stain, a cytogenetical stain, an in situ hybridization stain or a DNA stain. The claims are further drawn to one stain being a morphological stain and another stain being selected from an immunological stain, an

activity stain, an in situ hybridization stain and a DNA stain, one stain being a cytogenetical stain and another stain being selected from an immunological stain, an in situ hybridization stain and a DNA stain or one stain being a DNA stain and another stain being an in situ hybridization stain. Finally the claims are drawn to the imaging device being automated and capable of at least dual imaging.

The specification defines the "cytogenetical stain" as inclusive of the Giemsa stain; and it defines the "DNA stain" as a molecule that binds to chromosomes comprising DNA. See, e.g., page 13, lines 6-16.

As evidenced by Shimoni et al, the BIOVIEW DUET system is an automated microscope capable of dual imaging (see entire document, e.g., page 1413, second column).

As evidenced by Skacel et al., aberrations detected by FISH analysis identify transitional cell carcinoma cells, a type of bladder cancer (see entire document, e.g., page 382, first column).

Daniely et al teaches a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of the urine sample with two stains and imaging both stains with an automated microscope to identify transitional cell carcinoma cells or diagnose bladder cancer (see entire document). Daniely et al teaches staining cells obtained from urine samples with a Giemsa stain to look at morphology and a fluorescent in situ hybridization stain (FISH) and imaging the stains with the BioView Duet system (see, e.g., paragraphs 2-4). Daniely et al also teaches FISH analysis was used to scan samples for chromosome 3, 7, 9, and 17 aberrations (see, e.g., paragraph 4). Thus, Daniely et al teaches a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of the urine sample with two stains selected from a morphological, cytogenectical, DNA or an *in situ* hybridization stain and exposing said stained cells to two imaging modes in an automated device capable of dual imaging to identify transitional cell carcinoma cells or diagnose bladder cancer.

14. Claims 37-48, 52-53, 55-65 and 69-70 are rejected under 35 U.S.C. 102(b) as being anticipated by Skacel et al (Anal Quant Cytol Histol, 23(6): 381-387, December 2001).

The claims are drawn to a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of the urine sample with at least two stains and sequentially or simultaneously exposing said stained cells to at least two imaging modes to identify transitional cell carcinoma cells or diagnose bladder cancer. The claims are further drawn to the each of the stains being either a morphological stain, an immunological stain, a cytogenetical stain, an in situ hybridization stain or a DNA stain. The claims are further drawn to one stain being a morphological stain and another stain being selected from an immunological stain, an activity stain, an in situ hybridization stain and a DNA stain or one stain being a DNA stain and another stain being an *in situ* hybridization stain.

The specification defines the "DNA stain" as inclusive of the DAPI stain (see, e.g., page 14, line 31).

Skacel et al teaches a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of a urine sample with two stains and imaging both stains with a microscope to identify transitional cell carcinoma cells or diagnose bladder cancer (see entire document). In particular, Skacel et al teaches staining cells from voided urine with DAPI to look at morphology and a fluorescent *in situ* hybridization stain (FISH) and imaging the cells to identify and diagnose transitional cell carcinoma cells, a type of bladder cancer (see entire document, e.g., page 382 and 384). Thus, Skacel et al teach a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of the urine sample with two stains selected from a morphological, DNA or an in situ hybridization stain and exposing said stained cells to two imaging modes to identify transitional cell carcinoma cells or diagnose bladder cancer.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 37, 54, 55 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skacel et al (Anal Quant Cytol Histol, 23(6): 381-387, December 2001), in view of Daniely et al (Annales de Genetique, 46:153, September 2003).

The claims are drawn to a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells

of a urine sample with at least two stains and sequentially or simultaneously exposing said stained cells to at least two imaging modes to identify transitional cell carcinoma cells or diagnose bladder cancer. The claims are further drawn to the imaging device being automated and capable of at least dual imaging.

Skacel et al teaches that which is set forth in the above rejection of claims 37 and 55 under 35 U.S.C. 102(b).

Skacel et al does not expressly teach imaging the cells with an automated imaging device capable of dual imaging. This deficiency is made up for in the teachings of Daniely et al.

Daniely et al teach imaging cells from voided urine samples with the BioView Duet system (e.g. paragraph 3), which is an automated microscope capable of dual imaging as evidenced above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify transitional cell carcinoma cells or diagnose bladder cancer from a urine sample, by staining nucleated cells of a urine sample with at least two stains as taught in Skacel and imaging the stained cells with the automated microscope capable of dual imaging as taught by Daniely to identify transitional cell carcinoma cells or diagnose bladder cancer.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to identify transitional cell carcinoma cells or diagnose bladder cancer from a urine sample, by staining nucleated cells of a urine sample with at least two stains as taught in Skacel and imaging the stained cells with the automated microscope capable of dual imaging as taught by Daniely to identify transitional cell carcinoma cells or diagnose bladder cancer because as taught in Daniely, "the Bioview Duet system allows scanning the same slide several times while accumulating information from the different stains to each and every cell" (see paragraph 3). Thus, there would be an advantage and a reasonable expectation of success in identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, by staining nucleated cells of a urine

sample with at least two stains and imaging the stained cells with an automated microscope capable of dual imaging, in view of Skacel et al and Daniely et al.

18. Claims 37, 49-51, 54-55, 66-68 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skacel et al (Anal Quant Cytol Histol, 23(6): 381-387, December 2001), in view of US Patent 6,418,236 (Ellis et al, July 9, 2002).

The claims are drawn to a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells of a urine sample with at least two stains and sequentially or simultaneously exposing said stained cells to at least two imaging modes to identify transitional cell carcinoma cells or diagnose bladder cancer. The claims are further drawn to one stain being an immunological stain and another stain being selected from a morphological stain, an activity stain, an in situ hybridization stain and a DNA stain, one stain being an activity stain and another being selected from a morphological stain, an immunological stain, an in situ hybridization stain and a DNA stain, or one stain being a cytogenetical stain and another stain being an immunological stain, an in situ hybridization stain and a DNA stain. The claims are further drawn to the imaging device being automated and capable of at least dual imaging.

Skacel et al teaches that which is set forth in the above rejection of claims 37 and 55 under 35 U.S.C. 102(b).

Skacel et al does not expressly teach using an immunological stain, an activity stain or a cytogenetical stain in their method. Skacel et al also does not expressly teach imaging the cells with an automated imaging device capable of dual imaging.

US Patent 6,418,236 teaches automated image analysis using a microscope capable of dual imaging to image cells stained with two stains, wherein at least one stain is an immunological stain (immunohistochemistry stain), an activity stain (cytochemical stain) or a cytogenetical stain (Giemsa stain) (see entire document, e.g., column 1, lines 26-59, column 4, lines 31-37, column 5, lines 1-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify transitional cell carcinoma cells or

diagnose bladder cancer from a urine sample, by staining nucleated cells of a urine sample with at least two stains as taught in Skacel, wherein at least one stain of the two stains is an immunological stain, an activity stain or a cytogenetical stain and imaging the stained cells with the automated microscope capable of dual imaging as taught by US Patent 6,418,236 to identify transitional cell carcinoma cells or diagnose bladder cancer.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to identify transitional cell carcinoma cells or diagnose bladder cancer from a urine sample, by staining nucleated cells of a urine sample with at least two stains as taught in Skacel, wherein at least one stain of the two stains is an immunological stain, an activity stain or a cytogenetical stain and imaging the stained cells with the automated microscope capable of dual imaging as taught by US Patent 6,418,236 to identify transitional cell carcinoma cells or diagnose bladder cancer because immunological stains, activity stains and cytogenetical stain are known in the art and are commonly used to image cells as taught by US Patent 6,418,236. Furthermore, the automated imaging analysis "eliminates the need for operator input to locate biological objects or areas of interest for analysis" as taught by US Patent 6,418,236 (see column 8, lines 30-32). Thus, there would be an advantage and a reasonable expectation of success in identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, by staining nucleated cells of a urine sample with at least two stains, wherein at least one stain of the two stains is an immunological stain, an activity stain or a cytogenetical stain and imaging the stained cells with an automated microscope capable of dual imaging, in view of Skacel et al and US Patent 6,418,236.

19. Claims 37, 49-50, 55, and 66-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daniely et al (Annales de Genetique, 46:153, September 2003), in view of US Patent 6,418,236 (Ellis et al, July 9, 2002).

The claims are drawn to a method of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, comprising staining nucleated cells

of the urine sample with at least two stains and sequentially or simultaneously exposing said stained cells to at least two imaging modes to identify transitional cell carcinoma cells or diagnose bladder cancer. The claims are further drawn to one stain being an immunological stain and another stain being selected from a morphological stain, an activity stain, an in situ hybridization stain and a DNA stain or one stain being an activity stain and another stain being selected from a morphological stain, an immunological stain, an in situ hybridization stain and a DNA stain.

Daniely et al teaches that which is set forth in the above rejection of claims 37 and 55 under 35 U.S.C. 102(a).

Daniely et al does not expressly teach one of the stains being an immunological stain or an activity stain. These deficiencies are made up for in the teachings of US Patent 6,418,236.

US Patent 6,418,236 teaches image analysis using a microscope capable of dual imaging to image cells stained with two stains with at least one stain being an immunological stain (immunohistochemistry stain) or an activity stain (cytochemical stain). (see entire document, e.g., column 1, lines 26-59, column 4, lines 31-37, column 5, lines 1-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify transitional cell carcinoma cells or diagnose bladder cancer from a urine sample, by staining and imaging nucleated cells of a urine sample with at least two stains as taught in Daniely, wherein at least one stain of the two stains is an immunological stain or an activity stain as taught by US Patent 6,418,236 to identify transitional cell carcinoma cells or diagnose bladder cancer.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to identify transitional cell carcinoma cells or diagnose bladder cancer from a urine sample, by staining and imaging nucleated cells of a urine sample with at least two stains as taught in Daniely, wherein at least one stain of the two stains is an immunological stain or an activity stain as taught by US Patent 6,418,236 to identify transitional cell carcinoma cells or diagnose bladder cancer because immunological stains and activity stains are

known in the art and are commonly used to image cells as taught by US Patent 6,418,236. Furthermore, immunological stains and activity stains would have the advantage of looking at specific immunological markers for transitional cell carcinoma cells or bladder cancer and specific activity markers for transitional cell carcinoma cells or bladder cancer. Thus, there would be an advantage and a reasonable expectation of success in identifying transitional cell carcinoma cells or diagnosing bladder cancer from a urine sample, by staining nucleated cells of a urine sample with at least two stains, wherein at least one stain of the two stains is an immunological stain, an activity stain or a cytogenetical stain and imaging the stained cells with an automated microscope capable of dual imaging, in view of Daniely et al and US Patent 6,418,236.

Conclusion

20. No claim is allowed.

21. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Halling et al (Journal of Urology, 164:1768-1775, November 2000) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with DAPI and FISH stains. Bubendorf et al (Anatomic Pathology, 116:79-86, 2001) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with DAPI and FISH stains. Darzynkiewicz et al (Experimental Cell Research, 249:1-12, 1999) discloses an automated cell-imaging device capable of dual imaging.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

STEPHEN L. RAWLINGS, PH.D.
PRIMARY EXAMINER